REMARKS

Status of the Claims

Claims 2, 3 and 75-112 are pending in the application; claims 1 and 4-74 have been canceled, and claims 111-112 have been withdrawn. The Office Action indicated that claims 111-112 were also examined and rejected; however, the Applicants previously identified these claims as 'Withdrawn", so they should not have been subject to examination or rejection; the remarks below are consistent with that situation.

No claims are substantively amended at this time, but claims 2, 78, 99, 100 and 102 were amended to correct typographical errors that were noted.

Finality of the Office Action Mailed February 8, 2008 Was Improper

The Office Action mailed on February 8, 2008 was made final. According to the Office, "Applicant's amendment necessitated the new ground(s) of rejection…Accordingly THIS ACTION IS MADE FINAL. See MPEP § 706.07(a)."

The Applicants discussed this with the Examiner by phone on July 25, 2008, and the Examiner agreed to withdraw finality. The Applicants acknowledge this and thank the Examiner for his reconsideration of and agreement to withdraw finality.

Rejection Under 35 U.S.C. § 112, First Paragraph: Enablement

Claims 2-3 and 75-110 (all claims in examination) were rejected as allegedly lacking enablement, "because the specification, while being enabling for the specifically recited examples of Tables 1-3 of the specification for the compositions used *in vitro* with an HCV model does not reasonably provide enablement for the broadest interpretation of the base and subsequent claims, e.g., the use as a vaccine adjuvant with [sic] for the treatment and prevention of cancers and microbes *in vivo*…Use of vaccine adjuvants is still an empirical art requiring experimentation to optimize…" Office Action at page 3, emphasis added. The Applicants traverse this rejection.

The pending claims are composition claims. MPEP 2164.01(c) says this about a composition claim: "When a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. … In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention."

The enablement rejection discussed above focuses on the uses of the claimed compositions, and argues that Applicants have not enabled 'all possible uses' for all possible vaccines and all possible indications. However, the pending claims are composition claims, and are not limited by a recited use. Thus an enablement rejection is improper if any use commensurate in scope with the claims is enabled.

The Examiner indicated that the specification is enabling for certain uses, including the examples of Tables 1-3. These Tables relate to compounds demonstrated to have activity in an HCV model system. The Applicants note that the examples said to be enabled appear to include over 800 compounds corresponding to Formula I of claim 2. The Examiner recognized that the scope of the compounds of Formula I is enabled, and rejected the claims by alleging that the specification does not enable all possible uses of the compositions containing these compounds. This is improper: a composition is patentable regardless of whether all of its uses are described or even known. A claim to 'aspirin' is enabled by a disclosure that enables one to make aspirin as long as at least one use is known and enabled; patentability does not require enablement or even knowledge of all possible uses, because if it did, no compound claim would *ever* be allowable. Thus the claims as presented are believed to be enabled, because the compositions themselves are enabled (this was not questioned in the Office Action), and at least one enabled use (effectiveness on HCV) commensurate in scope with the scope of the compositions was acknowledged by the Examiner.

The Examiner discussed several references in this rejection, taking the position that the claims are not enabled because of unpredictability in the vaccine arts:

> Use of vaccine adjuvants is still an empirical art requiring experimentation to optimize antigen concentration, adjuvant concentration, routes of administration, etc. and must be performed for each antigen/antigen [sic: adjuvant?]/vaccinee species. Altman...notes that a universal vaccine formulation will not be available in the near future…Aucouturier teaches that there are no universal adjuvants…East provides that the mechanisms by which adjuvants promote the immune response are poorly understood…the author directs that it is clear that much more work needs to be done on the nature of immunopotentiation and adjuvant action before the skilled artisan can, with confidence, combine new generation antigens with appropriate adjuvants to make successful vaccines…Edelman teaches that adjuvant use remains largely empiric…antigens are best matched with adjuvants by means of a trial and error process of iterative experiments…McElrath teaches that the success of an adjuvant in clinical studies may not always be predictable from animal studies, and that adjuvant properties may differ according to the immunogen…Wiilson provides an example of trial with several adjuvants, showing that components known as an aduvant…[are] not necessarily effective as an adjuvant in another setting (abstract). Thus, a skilled artisan would be required to perform undue experimentation to practice the full scope of the invention.

First, the fact that a "universal adjuvant" remains elusive is not a proper standard for the enablement analysis. That standard would apparently require clinical efficacy for a single adjuvant with every conceivable antigen. The claims do not require any single compound to work with every conceivable antigen; indeed, the claims recite compositions having an amount of a compound of formula I effective to potentiate an immune response for an antigen, not for all possible antigens. Lack of efficacy with other antigens is not required.

Enablement should be assessed according to the *Wands* factors and standards. *In re Wands* (8 USPW2d 1400) states that "Enablement is not precluded by the necessity for some experimentation such as routine screening…the key word is 'undue,' not 'experimentation,'" and also says, "a considerable amount of experimentation is permissible, if it is merely routine." The court in *Wands* noted that the process of screening required to practice the antibody invention in its fact pattern were "well known in the monoclonal antibody art." Likewise, the methods for testing an adjuvant of the present claims with a particular antigen of interest are also well-known in the art. Altman describes experimental methods to select an immunostimulatory compound and carrier for a particular antigen (pp. 305-306), and the testing appears to be entirely routine. Indeed, all of the references that were cited by the Examiner recognize the need for empirical studies to identify the

specific adjuvant to be used with a particular antigen: it is clear that those skilled in the art recognize the need for experimentation.

Referring again to In re Wands, the court in that case took the position that all of the screening work to find an antibody is "the entire attempt to make a monoclonal antibody against a particular antigen." Even though that 'entire attempt' would include immunizing many mice, and screening many hybridomas that would mostly not work, that was considered a 'routine experiment' because the methods for doing it were known and those in the art expected to use such methods and to encounter more unsuccessful hybridoma tests than successful ones. Since the methods to perform the experimentation for the vaccine adjuvant compositions as claimed are also well known, and those of skill in the art expect to do screening of many combinations, such experimentation is neither *unexpected* nor *undue*; it is routine testing. As *Wands* says, "a considerable amount of experimentation is permissible, if it is merely routine." Here, some experimentation may be needed to identify which adjuvant increases the efficacy of an antigen for eliciting an immune response, but that experimentation is still routine.

Second, the fact that animal studies sometimes fail to predict clinical effectiveness in humans is irrelevant. The clear implication of that comment, and of continued use, by those skilled in the art, of animal studies to identify vaccine compositions for human testing demonstrate that animal studies are *generally* predictive. Patentability does not require a composition to be proven effective in clinical trials; it only requires evidence of activity in generally accepted *in vitro* test methods that reasonably correlate with *in vivo* use. Neither absolute predictability nor clinical activity is needed for patentability. The Examiner acknowledged that the large number of compounds in Tables 1-3 were enabled for use *in vitro* against HCV, and absent reason to doubt the existence of a correlation with *in vivo* use. Thus the large volume of *in vitro* activity data that was provided is sufficient to satisfy the enablement requirement, absent some reason to doubt that it correlates with *in vivo* effects.

Third, the fact that the mechanism of action of adjuvants is complex or unknown is not significant to the enablement analysis. Such mechanistic uncertainty is recognized by several of the

references cited by the Examiner (e.g., Altman and East), but it does not prevent one from using adjuvants, or even affect the types of experimentation required to select an adjuvant. Indeed, this evidence demonstrates that adjuvants are currently being used successfully, even without knowing how they work. The desired effect for compositions of the claims can be observed without needing to understand how it occurs. The application provides evidence tending to show effectiveness of a wide range of compounds of Formula I in an accepted model; in view of that, no mechanistic understanding is needed for one of ordinary skill to use the claimed invention.

The claims recite an effective amount of a compound of formula I to potentiate a cell-mediated response to an antigen. This functional limitation excludes compositions that do not contain sufficient compound of formula I to potentiate an immune reaction. Experimentation to select a particular adjuvant compound for a given antigen does not require an understanding of the mechanism by which the adjuvant works; and the cited references accept that such experimentation is normal in the vaccine arts for selecting an adjuvant to pair with a chosen antigen.

Wands says that enablement is "a conclusion reached by weighing many factual considerations." Here, there is a high level of skill in the relevant art; the application provides a substantial amount of guidance (ca. 800 active compounds); the art of pairing an adjuvant with an antigen for a vaccine is recognized as an empirical process; and that process uses well-known methods. Selection of the compound of Formula I and an amount of the compound to potentiate an immune response thus involves only routine experiments. Since such experimentation is expected and accepted as ordinary by those of skill in the art, and since the experiments use well-known methods, the claimed invention can be practiced without *undue* experimentation. Thus there is no need for *undue* experimentation to use the invention as claimed, and the invention as claimed is enabled under the *Wands* standards.

For these reasons, the Applicants respectfully request withdrawal of this rejection.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 223002107000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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